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(54) Title: RETINOL CONTAINING COSMETIC COMPOSITION (57) Abstract A composition for topical application to human skin in order to promote the repair of photo-damaged skin and/or to reduce or prevent the damaging effects of UV light on skin and/or to lighten the skin comprising retinol or a derivative thereof and a selected skin lightening agent.		

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RETINOL CONTAINING COSMETIC COMPOSITION

FIELD OF INVENTION

5 The invention relates to a composition for topical application to human skin in order to lighten skin colour and to promote the repair of photo-damaged skin and/or to reduce or prevent the damaging effects of ultra-violet light on skin. The invention also relates to the use of
10 such compositions in lightening skin colour, in the repair of photo-damaged skin and in the prevention of damage to skin due to exposure to ultra-violet light.

BACKGROUND TO THE INVENTION

15 The treatment of human skin damaged due to exposure to ultra-violet light, ie. photo-damage, has been subject to much research effort in recent years, particularly with the realisation that skin cancer and other skin disorders can
20 arise where the exposure to sunlight is excessive. This problem is even more serious with the depletion of the ozone layer which is believed to permit a higher level of ultra-violet radiation to reach the earth's surface.

25 Chronic exposure to sunlight results in multiple adverse effects on all structural elements of the skin. The clinical manifestation of these changes, collectively known as photoageing is lax, dry inelastic skin that is wrinkled and blotchy with a coarse, roughened texture, uneven colour
30 and altered pigmentation.

Skin blotchiness or mottling (hyperpigmentation) is due to changes in the melanocytes or the processing of melanin within the population of epidermal cells. These pigment
35 producing cells, which unlike the keratinocytes remain at the base of the epidermis, lose their normal regulation process with ageing and produce excess pigment. This leads

to the formation of dense perinuclear clumps of melanin in slowly turning over keratinocytes within the epidermis, and areas of hyperpigmentation or 'age spots' develop.

5 In the therapy of such hyperpigmented skin, certain skin lightening agents such as kojic acid, hydroquinone or ascorbic acid are effective by inhibiting the formation of melanin. Vitamin A acid (retinoic acid) is beneficial in hyperpigmentation problems by normalising the skin colour..

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Also by increasing cell turnover, Vitamin A acid prevents accumulation of pigment within the more rapidly dividing and migrating keratinocytes. Vitamin A acid also enhances the pigment reducing potential of conventional skin

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The topical application of Vitamin A acid does however have a major drawback in that it is a potent skin irritant, and can accordingly damage the skin. Vitamin A acid is also a

20 teratogen. Its recommended use for example as a prescription drug in the treatment of acne involves careful control, such that excessive doses are avoided in order to restrict the side effects which can occur with skin. By the same token, the use of Vitamin A acid for lightening

25 skin and in the treatment or prevention of photo-damaged skin is severely limited by these side effects, and for this reason it is not generally recommended for use in cosmetic products.

30

We have now discovered that retinol or certain derivatives thereof, when combined with a skin lightening agent can be used effectively in the repair of photo-damaged skin or the prevention of photo-damage to skin following exposure to ultra-violet light. This combination is also particularly

35 useful in reducing hyperpigmentation of skin.

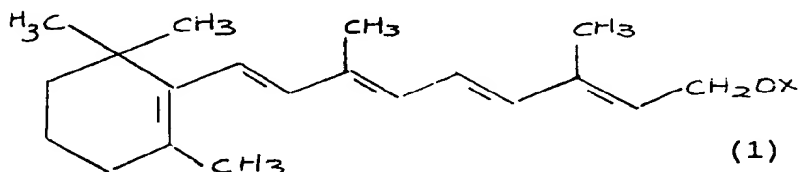
The invention is accordingly concerned with compositions

comprising retinol or certain derivatives thereof together with a skin lightening agent for topical application to human skin, and the use of this combination of active agents to lighten skin and in the treatment of photo-damaged and/or hyperpigmented skin or the prevention thereof, following excessive exposure to ultra-violet light.

DEFINITION OF THE INVENTION

Accordingly, the invention provides a composition suitable for topical application to human skin in order to lighten skin and promote repair of photo-damaged skin and/or to reduce or prevent the damaging effects of ultra-violet light on skin, which composition comprises:

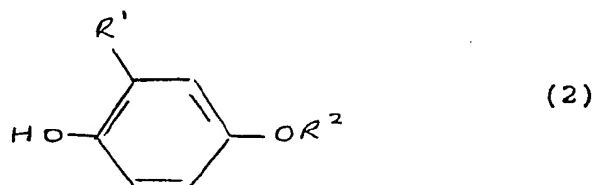
- i) an effective amount of from 0.001 to 10% by weight of retinol or a derivative thereof having the structure (1):



where X represents H or COR where R represents a group chosen from branched or unbranched, alkyl or alkenyl groups having an average of from 1 to 20 carbon atoms; and

- ii) an effective amount of from 0.01 to 20% by weight of a skin lightening agent chosen from L-ascorbic acid and derivatives thereof, kojic acid and derivatives

thereof, hydroquinone and derivatives thereof, extract of placenta, arbutin, niacin, niacinamide, α hydroxy acids, phloretin, phloridzin, liquorice extract, cysteaminyphenol and derivatives thereof and compounds having the structure (2):



15 where R^1 represents H, or an ether group represented by OR^3 ,

20 R^2 and R^3 are the same or different and each represents a group chosen from branched or unbranched alkyl or alkenyl groups having an average of from 1 to 20 carbon atoms.

DISCLOSURE OF THE INVENTION

25 Invention concerns a composition comprising retinol or a derivative thereof together with a skin lightening agent which together behave synergistically in lightening skin and reducing skin blotchiness and mottling due to hyperpigmentation. Furthermore, due to the rejuvenating influence of the retinol or its derivative on skin, there will be an overall improvement in skin texture with reduction in fine wrinkling and improved skin colour. Also, co-formulation with a sunscreen will enhance the photo stability and activity of retinol or its derivative within the formulation and also prevent further actinic damage to the skin.

35

Retinol and derivatives thereof

The composition according to the invention comprises retinol or a derivative thereof having the structure (1).

5

In addition to retinol itself, examples of derivatives of retinol include:

Retinyl acetate
10 Retinyl butyrate
Retinyl propionate
Retinyl octanoate
Retinyl laurate
Retinyl palmitate
15 Retinyl oleate
Retinyl linoleate.

The amount of retinol, or a derivative thereof, present in the composition according to the invention is from 0.001 to 10% and preferably 0.01 to 5% by weight of the composition.

20

Preferably the composition comprises retinol, most preferably the composition comprises the trans-isomer of retinol.

25

The skin lightening agent

The composition according to the invention also comprises a skin lightening agent.

30

Examples of skin lightening agents include:

L-ascorbic acid, and derivatives thereof
Kojic acid, and derivatives thereof
35 Hydroquinone and derivatives thereof
Extract of placenta
Compounds having the structure (2)

Arbutin
α hydroxy acids
phloretin
phloridzin,
5 liquorice extract
cysteaminyphenol and derivatives thereof
Niacin, and
Niacinamide.

10 Preferably the skin lightening agent is hydroquinone and derivatives thereof, most preferably hydroquinone.

The amount of skin lightening agent which is present in the composition according to the invention is from 0.01 to 20%,
15 preferably 0.1 to 10% by weight of the composition.

The Cosmetically Acceptable Vehicle

20 The composition according to the invention also comprises a cosmetically acceptable vehicle to act as a dilutant, dispersant or carrier for other materials present in the composition, so as to facilitate their distribution when the composition is applied to the skin.

25 Vehicles other than water can include liquid or solid emollients, solvents, humectants, thickeners and powders. Examples of each of these types of vehicle, which can be used singly or as mixtures of one or more vehicles, are as follows:

30 Emollients, such as stearyl alcohol, glyceryl monoricinoleate, mink oil, cetyl alcohol, isopropyl isostearate, stearic acid, isobutyl palmitate, isocetyl stearate, oleyl alcohol, isopropyl laurate, hexyl laurate,
35 decyl oleate, octadecan-2-ol, isocetyl alcohol, eicosanyl alcohol, behenyl alcohol, cetyl palmitate, silicone oils such as dimethylpolysiloxane, di-n-butyl sebacate,

isopropyl myristate, isopropyl palmitate, isopropyl stearate, butyl stearate, polyethylene glycol, triethylene glycol, lanolin, cocoa butter, corn oil, cotton seed oil, olive oil, palm kernel oil, rapeseed oil, safflower seed oil, evening primrose oil, soybean oil, sunflower seed oil, avocado oil, sesame seed oil, coconut oil, arachis oil, castor oil, acetylated lanolin alcohols, petroleum jelly, mineral oil, butyl myristate, isostearic acid, palmitic acid, isopropyl linoleate, lauryl lactate, myristyl lactate, decyl oleate, myristyl myristate;

Propellants, such as propane, butane, isobutane, dimethyl ether, carbon dioxide, nitrous oxide;

Solvents, such as ethyl alcohol, isopropanol, acetone, ethylene glycol monoethyl ether, diethylene glycol monobutyl ether, diethylene glycol monoethyl ether;

Powders, such as chalk, talc, fullers earth, kaolin, starch, gums, colloidal silica sodium polyacrylate, tetra alkyl and/or trialkyl aryl ammonium smectites, chemically modified magnesium aluminium silicate, organically modified montmorillonite clay, hydrated aluminium silicate, fumed silica, carboxyvinyl polymer, sodium carboxymethyl cellulose, ethylene glycol monostearate.

The cosmetically acceptable vehicle will usually form from 10 to 99.9%, preferably from 50 to 99% by weight of the emulsion, and can, in the absence of other cosmetic adjuncts, form the balance of the emulsion.

Organic sunscreens

The composition of the invention optionally can comprise an organic sunscreen further to enhance the benefit of the composition in providing protection from the harmful effects of excessive exposure to sunlight.

Examples of suitable organic sunscreens, when required, include those set out in Table 1 below, and mixtures thereof.

5 TABLE 1

	CTFA Name	Trade Name	Supplier

	Benzophenone-3	UVINUL M-40	BASF Chemical Co.
10	Benzophenone-4	UVINUL MS-40	BASF Chemical Co.
	Benzophenone-8	SPECRA-SORB UV-24	American Cyanamide
	DEA		
	Methoxycinnamate	BERNEL HYDRO	Bernel Chemical
15	Ethyl dihydroxy-		
	propyl-PABA	AMERSCREEN P	Amerchol Corp.
	Glyceryl PABA	NIPA G.M.P.A.	Nipa Labs.
	Homosalate	KEMESTER HMS	Hunko Chemical
	Methyl anthranilate	SUNAROME UVA	Felton Worldwide
20	Octocrylene	UVINUL N-539	BASF Chemical Co.
	Octyl dimethyl PABA	AMERSCOL	Amerchol Corp.
	Octyl methoxy-		
	cinnamate	PARSOL MCX	Bernel Chemical
	Octyl salicylate	SUNAROME WMO	Felton Worldwide
25	PABA	PABA	National Starch
	2-Phenyl-		
	benzimidazole-		
	-5-sulphonic acid	EUSOLEX 232	EM Industries
	TEA salicylate	SUNAROME W	Felton Worldwide
30	3-(4-methylbenzy-		
	lidene)-camphor	EUSOLEX 6300	EM Industries
	Benzophenone-1	UVINUL 400	BASF Chemical Co.

	Benzophenone-2	UVINUL D-50	BASF Chemical Co.
	Benzophenone-6	UVINUL D-49	BASF Chemical Co.
	Benzophenone-12	UVINUL 408	BASF Chemical Co.
5	4-Isopropyl		
	dibenzoyl methane	EUSOLEX 8020	EM Industries
	Butyl methoxy di-		
	benzoyl methane	PARSOL 1789	Givaudan Corp.
	Etocrylene	UVINUL N-35	BASF Chemical Co.

10

The composition of the invention can accordingly comprise from 0.1 to 10%, preferably from 1 to 5% by weight of an organic sunscreen material.

15

Inorganic sunscreen

20

The composition according to the invention optionally can also comprise as a sunscreen ultrafine titanium dioxide in either of two forms, namely water-dispersible titanium dioxide and oil-dispersible titanium dioxide.

25

Water-dispersible titanium dioxide is ultrafine titanium dioxide, the particles of which are uncoated or which are coated with a material to impart a hydrophilic surface property to the particles. Examples of such materials include aluminium oxide and aluminium silicate.

30

Oil-dispersible titanium dioxide is ultrafine titanium dioxide, the particles of which exhibit a hydrophobic surface property, and which, for this purpose, can be coated with metal soaps such as aluminium stearate, aluminium laurate or zinc stearate, or with organosilicone compounds.

35

By "ultrafine titanium dioxide" is meant particles of titanium dioxide having an average particle size of less than 100nm, preferably from 10 to 40nm and most preferably

from 15 to 25nm.

By topical application to the skin of a mixture of both water-dispersible ultrafine titanium dioxide and oil-dispersible ultrafine titanium dioxide, synergistically enhanced protection of the skin against the harmful effects of both UV-A and UV-B rays is achievable.

It is believed that this unexpected benefit is due to the deposition of each type of titanium dioxide on different regions of the skin surface, water-dispersible titanium dioxide being preferentially retained by hydrophilic regions of the skin's surface, while oil-dispersible titanium dioxide is retained preferentially by hydrophobic regions of the skin's surface. The combined overall effect is that more efficient physical coverage of the skin's surface is attainable and this can be demonstrated by measurement of the Sun Protection Factor (SPF).

In order to achieve the enhanced, synergistic benefit, as herein described, the weight ratio of water-dispersible titanium dioxide to oil-dispersible titanium dioxide should be from 1:4 to 4:1, preferably from 1:2 to 2:1 and ideally about equal weight proportions.

The total amount of titanium dioxide that can optionally can be incorporated in the composition according to the invention is from 1 to 25%, preferably from 2 to 10% and ideally from 3 to 7% by weight of the composition.

Other Inorganic Sunscreens

The emulsion of the invention optionally can comprise an inorganic sunscreen in addition to ultrafine titanium dioxide as herein defined.

Examples of other inorganic sunscreens include:

zinc oxide, having an average particle size of from 1 to 300nm,

iron oxide, having an average particle size of from 1 to 300nm,

silica, such as fumed silica, having an average particle size of from 1 to 100nm.

It should be noted that silica, when used as an ingredient in the emulsion according to the invention can provide protection from infra-red radiation.

OPTIONAL SKIN BENEFIT MATERIALS AND COSMETIC ADJUNCTS

A particularly convenient form of the composition according to the invention is an emulsion, in which case an oil or oily material will normally be present, together with an emulsifier to provide either a water-in-oil emulsion or an oil-in-water emulsion, depending largely on the average hydrophilic-lyophilic balance (HLB) of the emulsifier employed.

Oil or oily material

The composition according to the invention can optionally comprise one or more oils or other materials having the properties of an oil.

Examples of suitable oils include mineral oil and vegetable oils, and oil materials, such as those already proposed herein as emollients. Other oils or oily materials include silicone oils, both volatile and non-volatile, such as polydimethyl siloxanes.

The oil or oily material, when present for the purposes for forming an emulsion, will normally form up to 90%,

preferably from 10 to 80% by volume of the composition.

Emulsifier

5 The composition according to the invention can also optionally comprise one or more emulsifiers the choice of which will normally determine whether a water-in-oil or and oil-in-water emulsion is formed.

10 When a water-in-oil emulsion is required, the chosen emulsifier or emulsifiers should normally have an average HLB value of from 1 to 6. When an oil-in-water emulsion is required, a chosen emulsifier or emulsifiers should have an average HLB value of >6.

15 Examples of suitable emulsifiers are set below in Table 1 in which the chemical name of the emulsifiers is given together with an example of a trade name as commercially available, and the average HLB value.

20

Table 2

	Chemical Name	Trade Name HLB Value
25	of Emulsifier	-----
	Sorbitan trioleate	Arlacel 85 1.8
	Sorbitan tristearate	Span 65 2.1
	Glycerol monooleate	Aldo MD 2.7
30	Glycerol monostearate	Atmul 84S 2.8
	Glycerol monolaurate	Aldo MC 3.3
	Sorbitan sesquioleate	Arlacel 83 3.7
	Sorbitan monooleate	Arlacel 80 4.3
	Sorbitan monostearate	Arlacel 60 4.7
35	Poloxyethylene (2)	
	stearyl ether	Brij 72 4.9
	Poloxyethylene sorbitol	

13

	beeswax derivative	G-1702	5
	PEG 200 dilaurate	Emerest 2622	6.3
	Sorbitan monopalmitate	Arlacel 40	6.7
	Polyoxyethylene (3.5)		
5	nonyl phenol	Emulgen 903	7.8
	PEG 200 monostearate	Tegester PEG	
		200 MS	8.5
	Sorbitan monolaurate	Arlacel 200	8.6
	PEG 400 dioleate	Tegester PEG	
10		400-DO	8.8
	Polyoxyethylene (5)		
	monostearate	Ethofat 60-16	9.0
	Polyoxyethylene (4) sorbitan		
	monostearate	Tween 61	9.6
15	Polyoxyethylene (4) lauryl		
	ether	Brij 30	9.7
	Polyoxyethylene (5) sorbitan		
	monooleate	Tween 81	10.0
	PEG 300 monooleate	Neutronyx 834	10.4
20			
	Polyoxyethylene (20)		
	sorbitan tristearate	Tween 65	10.5
	Polyoxyethylene (20)		
	sorbitan trioleate	Tween 85	11.0
25	Polyoxyethylene (8)		
	monostearate	Myrj 45	11.1
	PEG 400 monooleate	Emerest 2646	11.7
	PEG 400 monostearate	Tegester PEG 400	11.9
	Polyoxyethylene 10		
30	monooleate	Ethofat 0/20	12.2
	Polyoxyethylene (10)		
	stearyl ether	Brij 76	12.4
	Polyoxyethylene (10)		
	cetyl ether	Brij 56	12.9
35	Polyoxyethylene (9.3)		
	octyl phenol	Triton X-100	13.0
	Polyoxyethylene (4)		

14

	sorbitan monolaurate	Tween 21	13.3
	PEG 600 monooleate	Emerest 2660	13.7
	PEG 1000 dilaurate	Kessco	13.9
	Polyoxyethylene sorbitol		
5	lanolin derivative	G-1441	14.0
	Polyoxyethylene (12)		
	lauryl ether	Ethosperse LA-12	14.4
	PEG 1500 dioleate	Pegosperse 1500	14.6
	Polyoxyethylene (14)		
10	laurate	Arosurf HFL-714	14.8
	Polyoxyethylene (20)		
	sorbitan monostearate	Tween	14.9
	Polyoxyethylene 20 sorbitan monooleate	Tween 80	15.0
15	Polyoxyethylene (20) stearyl ether	Brij 78	15.3
	Polyoxyethylene (20)		
	sorbitan monopalmitate	Tween 40	15.6
20	Polyoxyethylene (20) cetyl ether	Brij 58	15.7
	Polyoxyethylene (25)		
	oxypropylene monostearate	G-2162	16.0
25	Polyoxyethylene (20)		
	sorbitol monolaurate	Tween 20	16.7
	Polyoxyethylene (23)		
	lauryl ether	Brij 35	16.9
	Polyoxyethylene (50)		
30	monostearate	Myrj 53	17.9
	PEG 4000 monostearate	Pegosperse 4000	
		MS	18.7

35 The foregoing list of emulsifiers is not intended to be limiting and merely exemplifies selected emulsifiers which are suitable for use in accordance with the invention.

It is to be understood that two or more emulsifiers can be employed if desired.

The amount of emulsifier or mixtures thereof, that optionally can be incorporated in the composition of the invention is from 1 to 50%, preferably from 2 to 20% and most preferably from 2 to 10% by weight of the composition.

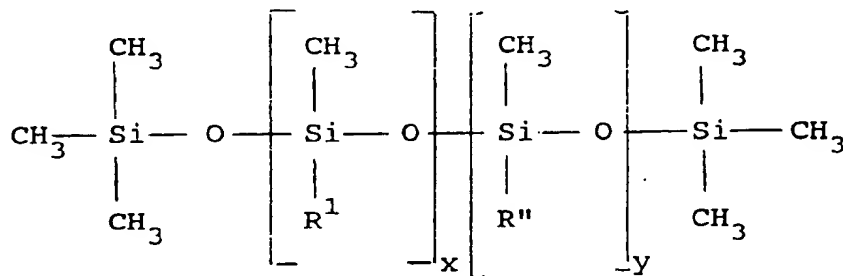
Water

The composition of the invention can also comprise water, usually up to 80%, preferably from 5 to 80% by volume.

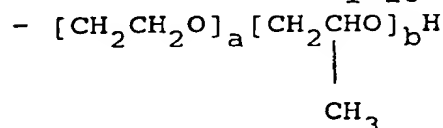
Silicone Surfactant

The composition of the invention can also optionally comprise a high molecular weight silicone surfactant which can also act as an emulsifier, in place of or in addition to the optional emulsifier(s) already mentioned.

The silicone surfactant is a high molecular weight polymer of dimethyl polysiloxane with polyoxyethylene and/or polyoxypropylene side chains having a molecular weight of from 10,000 to 50,000 and having the structure:



where the groups R' and R'' are each chosen from -H, C₁₋₁₈ alkyl and



a has a value of from 9 to 115,
b has a value of from 0 to 50,
x has a value of from 133 to 673,

5 y has a value of from 25 to 0.25.

Preferably, the dimethyl polysiloxane polymer is one in which:

10 a has a value of from 10 to 114
b has a value of from 0 to 49
x has a value of from 388 to 402
y has a value of from 15 to 0.75

15 one of groups R' and R" being lauryl, and the other having a molecular weight of from 1000 to 5000.

A particularly preferred dimethyl polysiloxane polymer is one in which:

20 a has the value 14
b has the value 13
x has the value 249
y has the value 1.25

25 The dimethyl polysiloxane polymer is conveniently provided as a dispersion in a volatile siloxane, the dispersion comprising, for example, from 1 to 20% by volume of the polymer and from 80 to 99% by volume of the volatile
30 siloxane. Ideally, the dispersion consists of a 10% by volume of the polymer dispersed in the volatile siloxane.

Examples of the volatile siloxanes in which the polysiloxane polymer can be dispersed include polydimethyl
35 siloxane (pentamer and/or hexamer).

A particularly preferred silicone surfactant is

cyclomethicone and dimethicone copolyol, such as DC 3225C Formulation Aid available from DOW CORNING. Another is laurylmethicone copolyol, such as DC Q2-5200, also available from Dow Corning.

5

The amount of silicone surfactant, when present in the composition will normally be up to 25%, preferably from 0.5 to 15% by weight of the emulsion.

10

Other Cosmetic Adjuncts

15

Examples of conventional adjuncts which can optionally be employed include preservatives, such as para-hydroxy benzoate esters; antioxidants, such butyl hydroxy toluene; humectants, such as glycerol, sorbitol, 2-pyrrolidone-5-carboxylate, dibutylphthalate, gelatin, polyethylene glycol, such as PEG 200-600; buffers, such as lactic acid together with a base such as triethanolamine or sodium hydroxide; waxes, such as beeswax, ozokerite wax, paraffin wax; plant extracts, such as Aloe vera, cornflower, witch hazel, elderflower, cucumber; thickeners; activity enhancers; colourants; and perfumes. Cosmetic adjuncts can form the balance of the composition.

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25

Use of the Composition

30

The composition according to the invention is intended primarily as a skin care product for topical application to human skin to lighten skin and/or to repair photo-damaged skin and to prevent photo-damage to skin due to exposure to sunlight. In particular, the composition can be used to reduce skin blotchiness and mottling due to hyperpigmentation, to improve skin texture with reductions in fine wrinkling and otherwise to improve skin colour. In general, the composition, when topically applied to skin, is useful in the prevention of actinic damage to all epidermal cells.

35

In use, a small quantity of the composition, for example from 1 to 5ml, is applied to exposed areas of the skin, from a suitable container or applicator and, if necessary, it is then spread over and/or rubbed into the skin using the hand or fingers or a suitable device.

PRODUCT FORM AND PACKAGING

The topical skin treatment composition of the invention can be formulated as a lotion having a viscosity of from 4,000 to 10,000 mPas, a fluid cream having a viscosity of from 10,000 to 20,000 mPas or a cream having a viscosity of from 20,000 to 100,000 mPas, or above. The composition can be packaged in a suitable container to suit its viscosity and intended use by the consumer.

For example, a lotion or fluid cream can be packaged in a bottle or a roll-ball applicator or a propellant-driven aerosol device or a container fitted with a pump suitable for finger operation. When the composition is a cream, it can simply be stored in a non-deformable bottle or squeeze container, such as a tube or a lidded jar.

The invention accordingly also provides a closed container containing a cosmetically acceptable composition as herein defined.

Test method - In vitro melanocyte cell culture

Pigment producing cells derived from a mammalian melanoma are grown in culture by standard methods. Preferred cell lines are B16 or S-91 cells, but other lines or primary mouse or human melanocytes can be used.

Melanoma cells are grown in cell culture medium such as RPMI 1640 (GIBCO) supplemented with fetal calf serum and glutamine to approximately 1/3 confluence. The active is

dissolved in culture medium, the pH adjusted as required and sterile filtered. The solution is then added to the cells.

5 The cells are cultured for a further period of 4 days and the amount of melanin produced assayed by measuring the absorbance at 540 nm of the melanin released into the medium.

10 Cell viability is tested using neutral red (3-amino-7-dimethylamino-2-methyl phenazine hydrochloride) a water soluble vital dye which passes through the intact plasma membrane and becomes concentrated in lysosomes of viable cells. For any culture, the amount of dye taken up is
15 proportional to the number of viable cells and agents that damage cell and lysosomal membranes inhibit dye incorporation.

The cells are incubated in 50 µg/ml neutral red solution
20 for 3 hours at 37°C in 5% CO₂ in air. The solution is aspirated, the cells washed once in saline and to them added a solvent (50% H₂O, 49% ethanol, 1% acetic acid) to solubilise the dye. The amount of neutral red dye is quantified by measuring absorbance at 540 nm.

25

Results

The above procedure was used to assess the ability of compositions of skin lightening agents (at a range of
30 concentrations) and retinol (at a range of concentrations) to reduce the amount of melanin produced without affecting cell viability.

These compositions were compared with compositions having
35 retinol alone at a range of concentrations and skin lightening agents alone at a range of concentrations.

The results for both viability and melanin production were calculated as percentages of the control which contained medium alone. Results are given in Table 3 and 4.

5 Results clearly show that the skin lightening agents and retinol act synergistically to reduce melanin production. There were no effects on cell viability at these concentrations.

10

Table 3

Trans retinol (μM)	Hydroquinone (mM)			
	0	0.001	0.0025	0.005
0	100	101.1	100.1	49.8*
2.0	115.3*	69.3*	40.7*	15.8*
6.7	87.5*	15.1*	14.8*	10.1*

20

* percentage is significantly different ($P < 0.05$) from control.

25

Table 4

Trans Retinol (M)	Kojic Acid (mM)		
	0.01	0.1	1
10^{-6}	78	73	8

30

EXAMPLES

35

The invention is further illustrated by the following examples; in each formulation, the titanium dioxide employed was ultrafine titanium dioxide having a mean particle size of from 15 to 25nm.

40

Example 1

This example illustrates a lotion according to the invention.

5

<u>Ingredient</u>	<u>% w/w</u>
retinyl propionate	1
kojic acid	1
10 silicone surfactant	10
volatile siloxane	14
mineral oil	1.5
titanium dioxide (water-dispersible)	2.5
titanium dioxide (oil-dispersible)	2.5
15 2-hydroxy octanoic acid	1
2-hydroxy propanoic acid	5
butylene glycol	10
sodium chloride	2
1-proline	0.1
20 neutralising agent	qs
preservative	qs
perfume	qs
water	qs

25

Example 2

5 This example illustrates a fluid cream according to the invention.

	<u>Ingredient</u>	<u>% w/w</u>
10	retinyl acetate	0.3
	niacinamide	1
	volatile siloxane (DC 345)	8.2
	silicone surfactant (DC 3225C)	12
	petroleum jelly	0.5
15	mineral oil	1.5
	Parsol MCX (octyl methoxycinnamate)	3
	titanium dioxide (oil-dispersible)	2
	titanium dioxide (water-dispersible)	2
	sodium chloride	2
20	butylene glycol	10
	l-proline	0.1
	2-hydroxy octanoic acid	1
	2-hydroxy propanoic acid	5
	neutralising agent	qs
25	preservative	qs
	perfume	qs
	water	qs

Example 3

This example illustrates a cream according to the invention.

5

<u>Ingredient</u>	<u>% w/w</u>
retinyl palmitate	1
L-ascorbic acid	2
10 volatile siloxane (DC 345 Fluid)	8.2
silicone surfactant (DC 3225C)	12
mineral oil	1.5
petroleum jelly	0.5
Parsol MCX (octyl methoxycinnamate)	1.5
15 titanium dioxide (oil-dispersible)	1.0
titanium dioxide (water-dispersible)	1
2-hydroxyoctanoic acid	1
2-hydroxypropanoic acid	5
sodium chloride	2
20 butylene glycol	10
l-proline	0.1
neutralising agent (aqueous phase to 4.5)	q.s.
preservative	q.s.
perfume	q.s.
25 water	to 100

Example 4

This example illustrates a lotion according to the invention.

5

<u>Ingredient</u>	<u>% w/w</u>
retinyl linoleate	0.5
retinyl palmitate	0.5
10 arbutin	2
silicone surfactant (DC 3225C)	10
volatile siloxane (DC 345)	14
mineral oil	1.5
Parsol MCX	3
15 titanium dioxide (oil-dispersible)	2
titanium dioxide (water-dispersible)	2
butylene glycol	10
sodium chloride	2
1-proline	0.1
20 2-hydroxy octanoic acid	1
2-hydroxy propanoic acid	5
neutralising agent	qs
perfume	qs
preservative	qs
25 water	qs

Example 5

This example illustrates a sunscreen cream in accordance with the invention.

5

<u>Ingredient</u>		<u>% w/w</u>
	retinyl oleate	2
	retinyl acetate	1
10	hydroquinone	1
	Polyoxyethylene (2) stearyl alcohol	3
	Polyoxyethylene (21) stearyl alcohol	2
	cetyl alcohol	1.5
	soft white paraffin	1.5
15	silicone fluid 200	5
	liquid paraffin	8
	glycerin	2
	preservatives	0.5
	titanium dioxide (water-dispersible)	2.5
20	titanium dioxide (oil-dispersible)	2.5
	water	to 100

Example 6

This example also illustrates a sunscreen cream in accordance with the invention.

5			
	<u>Ingredients</u>		<u>% w/w</u>
	retinyl acetate		0.2
	retinyl laurate		2
10	niacin		2
	cetyl dimethicone copolyol)	
	cetyl dimethicone) *	5
	polyglyceryl-3-oleate)	
	hexyl laurate)	
15	isopropyl myristate		13.5
	beeswax		3
	silicone fluid 200		5
	preservatives		0.5
20	titanium dioxide (water-dispersible)		2.5
	titanium dioxide (oil-dispersible)		2.5
	water		to 100

*Available is ABIL W508 ex Goldschmidt

Example 7

This example illustrates a lotion according to the invention.

5

Ingredient% w/w

	retinyl octanoate	2
	phloretin	2
10	silicone surfactant	10
	volatile siloxane	14
	mineral oil	1.5
	ultrafine titanium dioxide	
	(water-dispersible)	5
15	2-hydroxy octanoic acid	1
	2-hydroxy propanoic acid	5
	butylene glycol	10
	sodium chloride	2
	amino acid	0.1
20	neutralising agent	qs
	preservative	qs
	perfume	qs
	water	qs

Example 8

This example illustrates a lotion according to the invention.

5

<u>Ingredient</u>		<u>% w/w</u>
	retinyl palmitate	2
	hydroquinone monomethyl ether	0.5
10	silicone surfactant	10
	volatile siloxane	14
	mineral oil	1.5
	ultrafine titanium dioxide	
	(oil-dispersible)	5
15	2-hydroxy octanoic acid	1
	2-hydroxy propanoic acid	5
	butylene glycol	10
	sodium chloride	2
	amino acid	0.1
20	neutralising agent	qs
	preservative	qs
	perfume	qs
	water	qs

Example 9

This example illustrates a lotion according to the invention.

5	<u>Ingredient</u>	<u>% w/w</u>
	retinyl octanoate	1
	retinyl linoleate	1
10	phloridzin	1
	silicone surfactant	10
	volatile siloxane	14
	mineral oil	1.5
	ultrafine titanium dioxide	
15	(water-dispersible)	2.5
	ultrafine titanium dioxide	
	(oil-dispersible)	2.50
	2-hydroxy octanoic acid	1
	2-hydroxy propanoic acid	5
20	butylene glycol	10
	sodium chloride	2
	amino acid	0.1
	neutralising agent	qs
	preservative	qs
25	perfume	qs
	water	qs

Example 10

This example illustrates an anhydrous formulation in accordance with the invention.

5

Ingredient% w/w

retinol

0.2

4-S-cysteaminyphenol

1

10

Iso-propyl alcohol

10

volatile silicone

80

ethyl hexyl palmitate

8.7

antioxidant

0.1

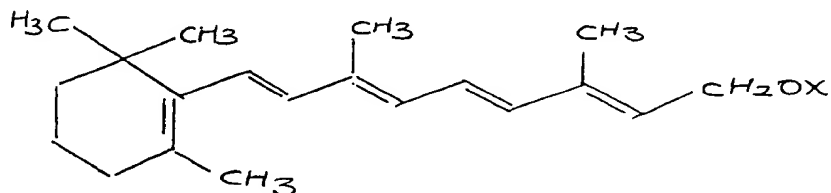
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CLAIMS

5 1. A composition suitable for topical application to human skin in order to promote repair of photo-damaged skin and/or to reduce or prevent the damaging effects of ultra-violet light on skin, which composition comprises:

10 i) an effective amount of from 0.001 to 10% by weight of retinol or a derivative thereof having the structure (1):

15

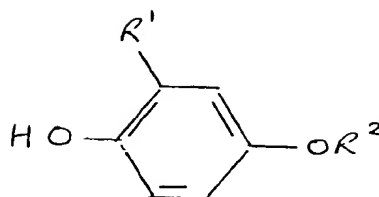


20

25 where X represents H or -COR where R represents a group chosen from branched or unbranched, alkyl or alkenyl groups having an average of from 1 to 20 carbon atoms; and

30 ii) an effective amount of from 0.01 to 20% by weight of a skin lightening agent chosen from L-ascorbic acid and derivatives thereof, kojic acid and derivatives thereof, hydroquinone and derivatives thereof, extract of placenta, arbutin, niacin, niacinamide, α hydroxy acids, phloretin, phloridzin, liquorice extract, cysteaminyphenol and derivatives thereof and compounds having the structure (2):

35



5

where R¹ represents H, or an ether group represented by OR³,

10

R² and R³ are the same or different and each represents a group chosen from branched or unbranched alkyl or alkenyl groups having an average of from 1 to 20 carbon atoms.

15

2. A composition according to claim 1 wherein the amount of retinol or a derivative thereof having the structure (1) is from 0.01 to 5% by weight of the composition.

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3. A composition according to claim 1 or 2 wherein the amount the skin lightening agent is from 0.1 to 10% by weight of the composition.

25

4. A composition according to any preceding claim wherein the skin lightening agent is hydroquinone or a derivative thereof.

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5. A composition according to any preceding claim wherein the skin lightening agent is hydroquinone.

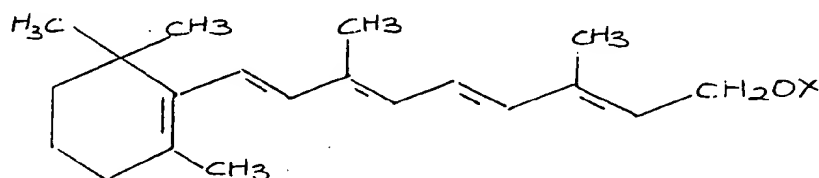
6. A composition according to any preceding claim wherein the composition comprises trans-retinol.

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7. Use of a composition according to any preceding claim in the repair of photo-damaged skin and/or in the prevention of damage to the skin due to exposure to ultraviolet light.

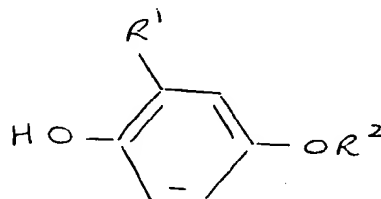
8. A method of reducing or preventing the damaging effects of UV light on skin and/or of lightening the skin, which method includes the topical application of a composition comprising:

- i) an effective amount of from 0.001 to 10% by weight of retinol or a derivative thereof having the structure (1):



where X represents H or -COR where R represents a group chosen from branched or unbranched, alkyl or alkenyl groups having an average of from 1 to 20 carbon atoms; and

- ii) an effective amount of from 0.01 to 20% by weight of a skin lightening agent chosen from L-ascorbic acid and derivatives thereof, kojic acid and derivatives thereof, hydroquinone and derivatives thereof, extract of placenta, arbutin, niacin, niacinamide, α hydroxy acids, phloretin, phloridzin, liquorice extract, cysteaminyphenol and derivatives thereof, and compounds having the structure (2):



(2)

where R^1 represents H, or an ether group represented by OR^3 ,

R^2 and R^3 are the same or different and each represents a group chosen from branched or unbranched alkyl or alkenyl groups having an average of from 1 to 20 carbon atoms.

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INTERNATIONAL SEARCH REPORT

Int. l. Application No
PCT/EP 93/03064

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61K7/48 A61K7/42

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	EP, A, 0 512 814 (UNILEVER PLC) 11 November 1992 see page 3, line 10 - line 58 see page 4, line 1 - line 9 see page 6, line 50 - line 58 see page 11, line 36 - line 47 see claims 1-3, 7-10; examples 4, 6, 8, 10, 13 ---	1-8
P, X	WO, A, 93 00085 (JOHNSON & JOHNSON CONSUMER PRODUCTS) 7 January 1993 see claims 1-5, 8; examples 5, 6, 14 --- -/--	1-3, 6-8

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- * & * document member of the same patent family

Date of the actual completion of the international search

11 January 1994

Date of mailing of the international search report

18. 01. 94

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INTERNATIONAL SEARCH REPORT

International Application No
CT/EP 93/03064

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	DATABASE WPI Week 9334, Derwent Publications Ltd., London, GB; AN 93269739 & JP,5 186 324 (SUNSTAR CHEM IND) 27 July 1993 see abstract ---	1-3,7,8
X	DATABASE WPI Week 9208, Derwent Publications Ltd., London, GB; AN 92062027 & JP,A,4 009 325 (SUNSTAR KK) 14 January 1992 see abstract ---	1,8
A	PATENT ABSTRACTS OF JAPAN vol. 13, no. 472 (C-647)25 January 1989 & JP,A,01 186 811 (SUNSTAR INC) 26 July 1989 see abstract ---	1-6
A	EP,A,0 470 275 (SUNSTAR KABUSHIKI KAISHA) 12 February 1992 see table 1 -----	1-8

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 93/03064

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
REMARK: ALTHOUGH CLAIM 8 IS DIRECTED TO A METHOD OF TREATMENT OF THE HUMAN BODY THE SEARCH HAS BEEN CARRIED OUT AND BASED ON THE ALLEGED EFFECTS OF THE COMPOSITION.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 93/03064

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0512814	11-11-92	NONE	
WO-A-9300085	07-01-93	AU-A- 8299791	25-01-93
		CA-A- 2090104	28-12-92
		EP-A- 0549592	07-07-93
EP-A-0470275	12-02-92	JP-A- 2207013	16-08-90